TWELVE (12) SHEETS OF FORMAL
SUBSTITUTE DRAWINGS
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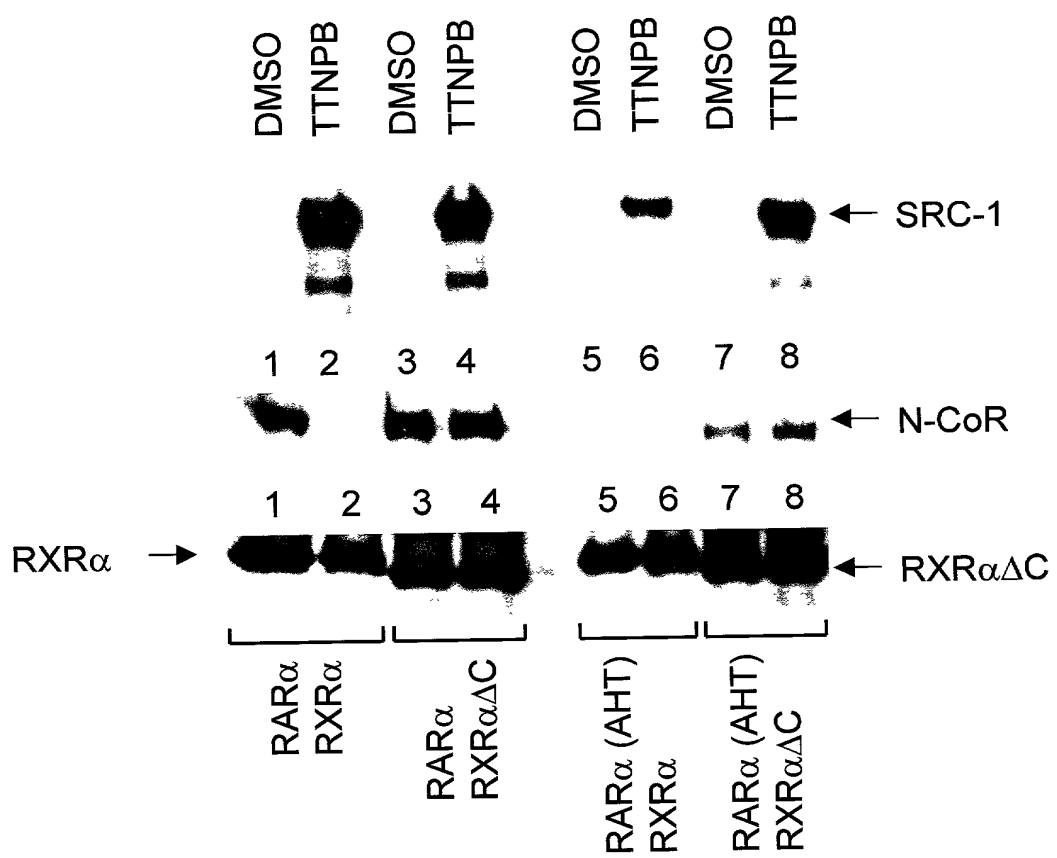
August 3, 2001
Date of Signature

DMSO
TTNPB
DMSO
TTNPB
DMSO
TTNPB
DMSO
TTNPB

← SRC-1

1 2   3 4   5 6   7 8

← N-CoR

1 2   3 4   5 6   7 8

RXRα →   ← RXRαΔC

RARα
RXRα

RARα
RXRαΔC

RARα (AHT)
RXRα

RARα (AHT)
RXRαΔC

FIG.1

DMSO TTNPB

RARα (wt) : + - + -
RARα (R272-A) : - + - +

← N-CoR

← SRC-1

← RXR

1 2 3 4

FIG.2A

SRC-1   N-CoR

| wt | E412-R | E412-A | K262-A | R272-A | | wt | E412-R | E412-A | K262-A | R272-A |

DMSO

TTNPB

196382

1   2   3   4   5   6   7   8   9   10
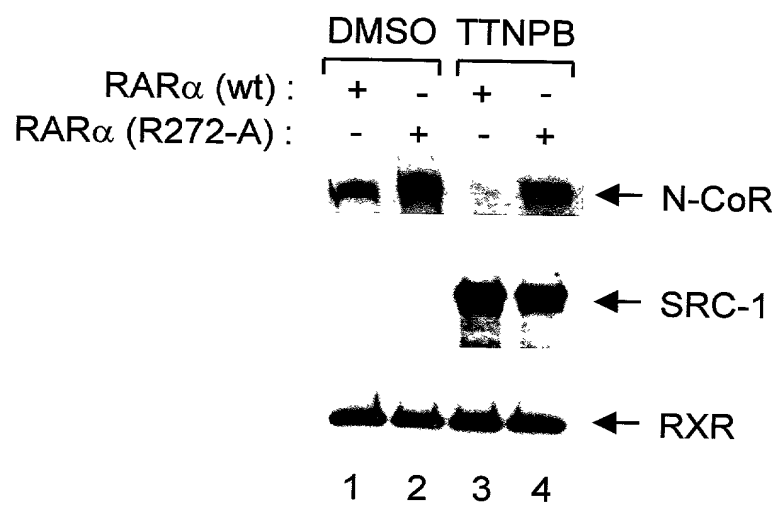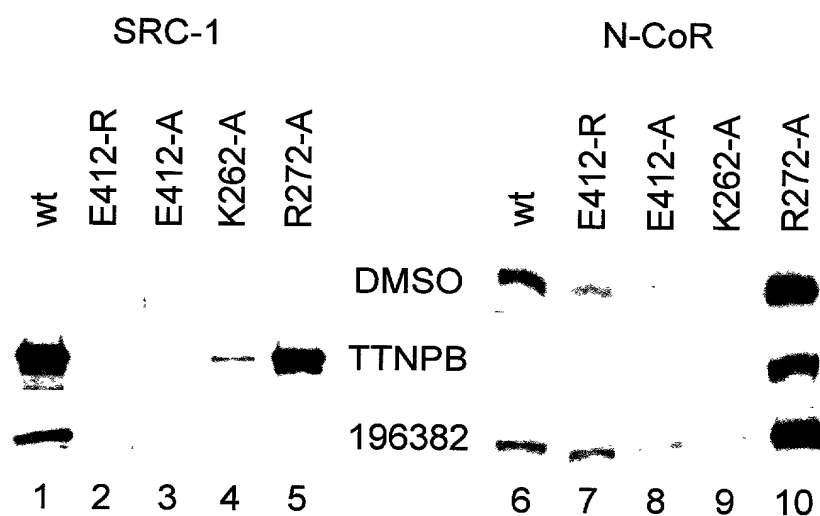
FIG.2B

ER-RAR-α
CHIMERIC ASSAY-NORMALIZED
BIOMEK-OPAQUE

○ TTNPB 126BK
□ 4365 15AC
△ 4794 181BK
▽ 6412 15AC
◇ 6382 15AC

NOTE: 1X 10^{-6}M USED AS A MAX @ α, β, γ

% RESPONSE (ATRA)

LOG [M]

FIG. 3A

FIG.3B

RARα VS RARα (R272-A)

● 1183 @ RAR
■ 6382 @ RAR
○ 1183 @ R272-A
□ 6382 @ R272-A

LOG [M]

LUCIFERASE ACTIVITY

FIG.4

WT R_{272}-A

0   10^{-9} 10^{-8} 10^{-7} 10^{-6} 0 10^{-9} 10^{-8} 10^{-7} 10^{-6}

SRC-1 →

1   2   3   4   5   6   7   8   9   10

FIG.5A

FIG.5B

FIG.6

% INHIBITION

LOG [M]

■ AGN 191183
▼ AGN 194365
◆ AGN 194794
◇ AGN 196382
○ AGN 196412
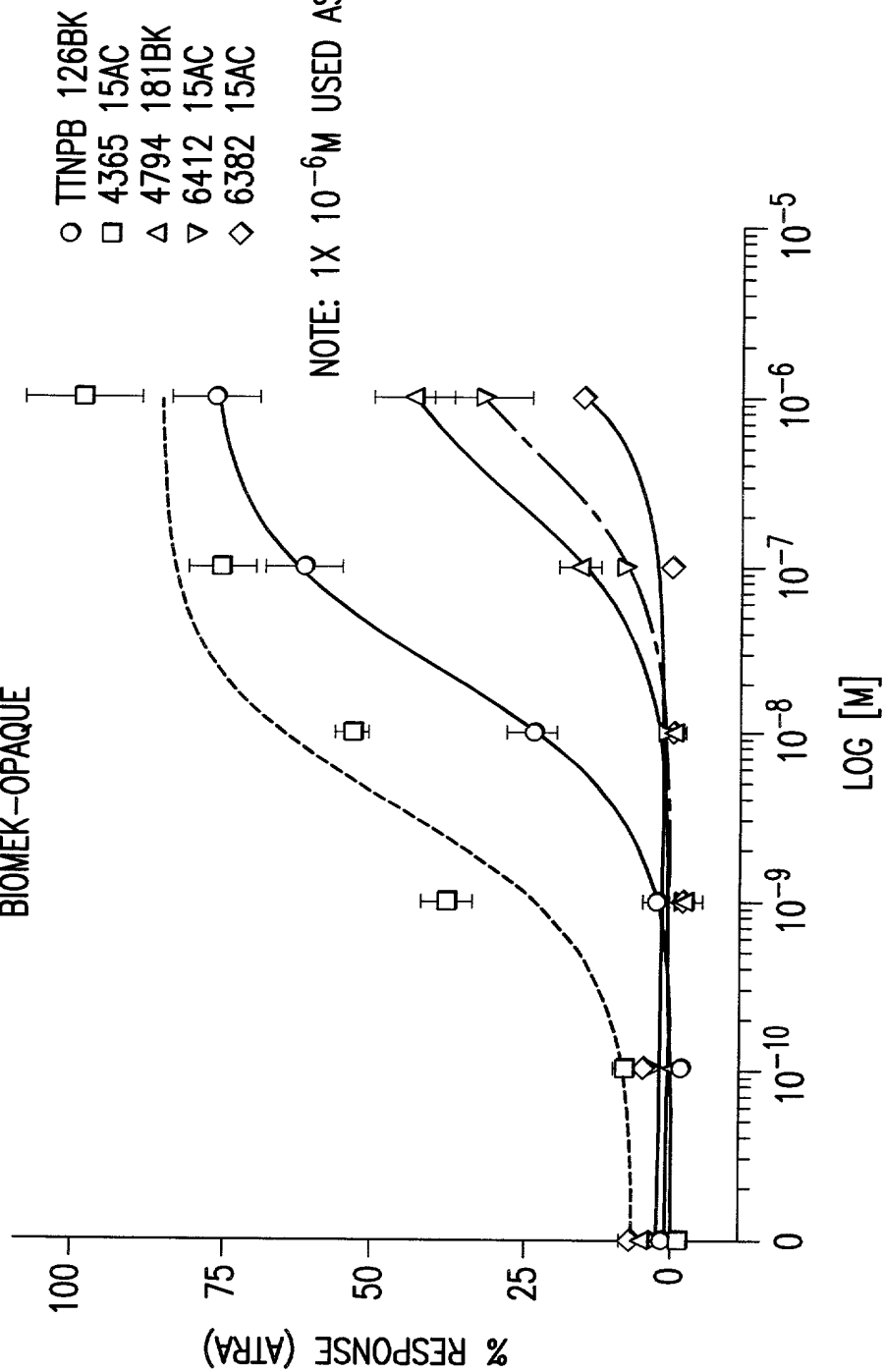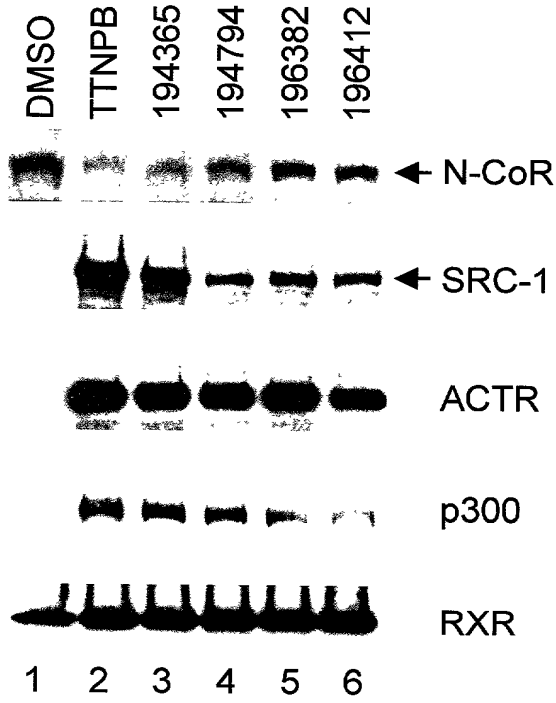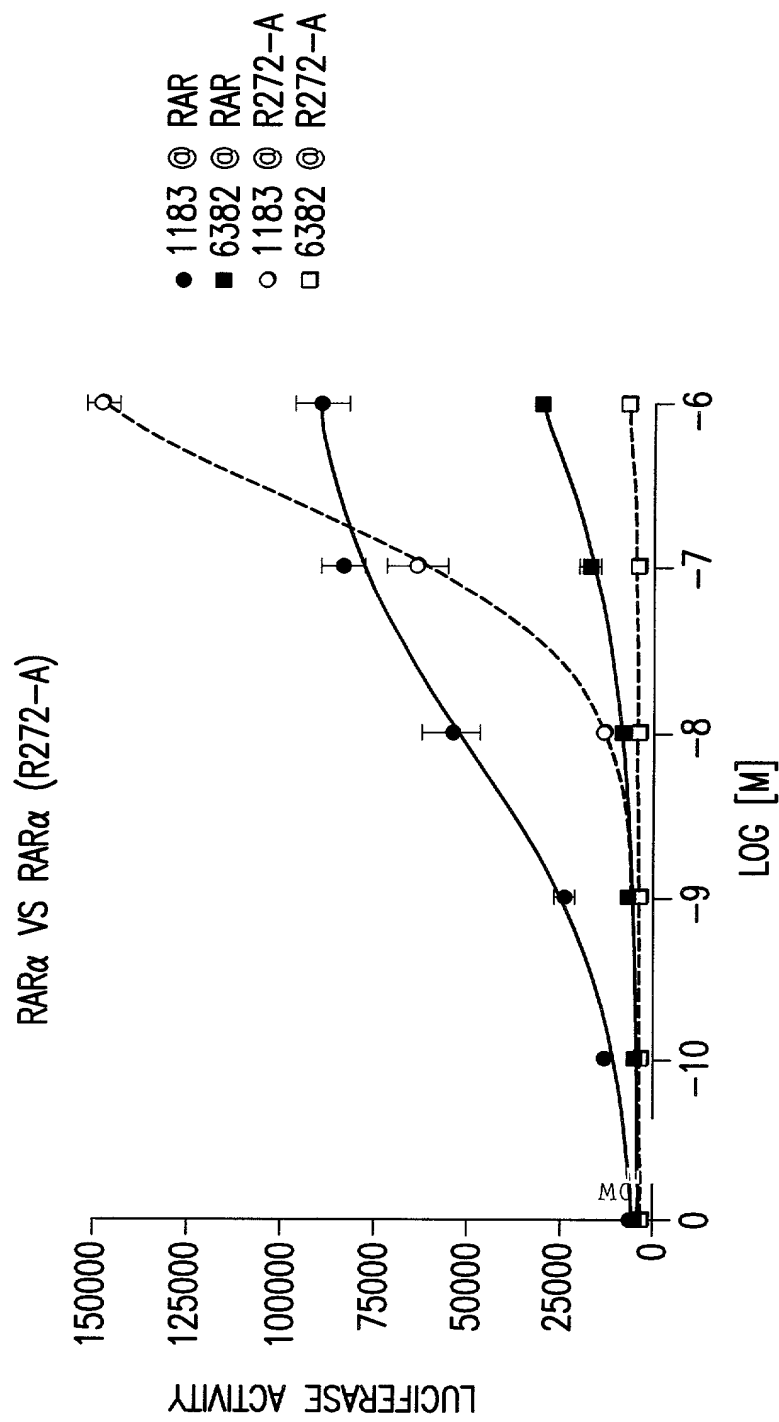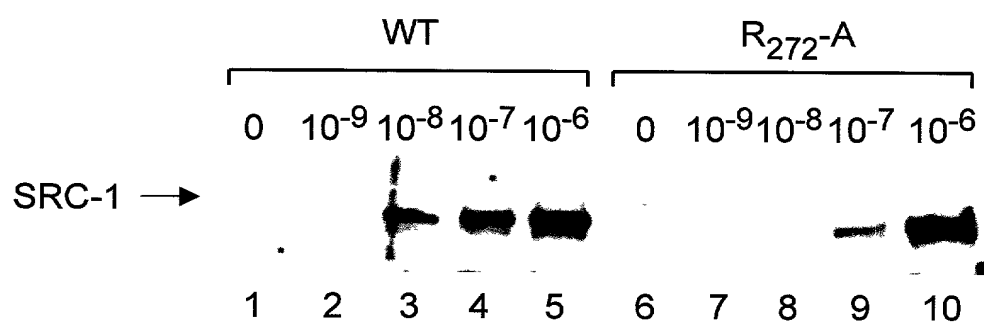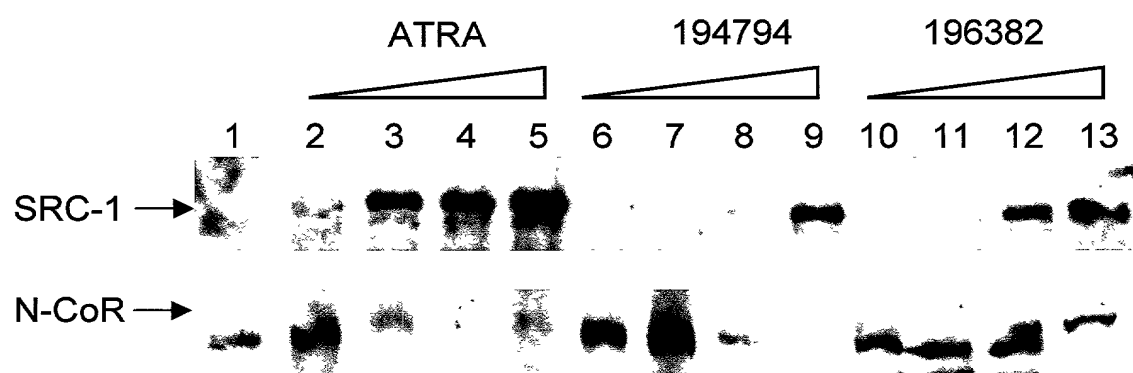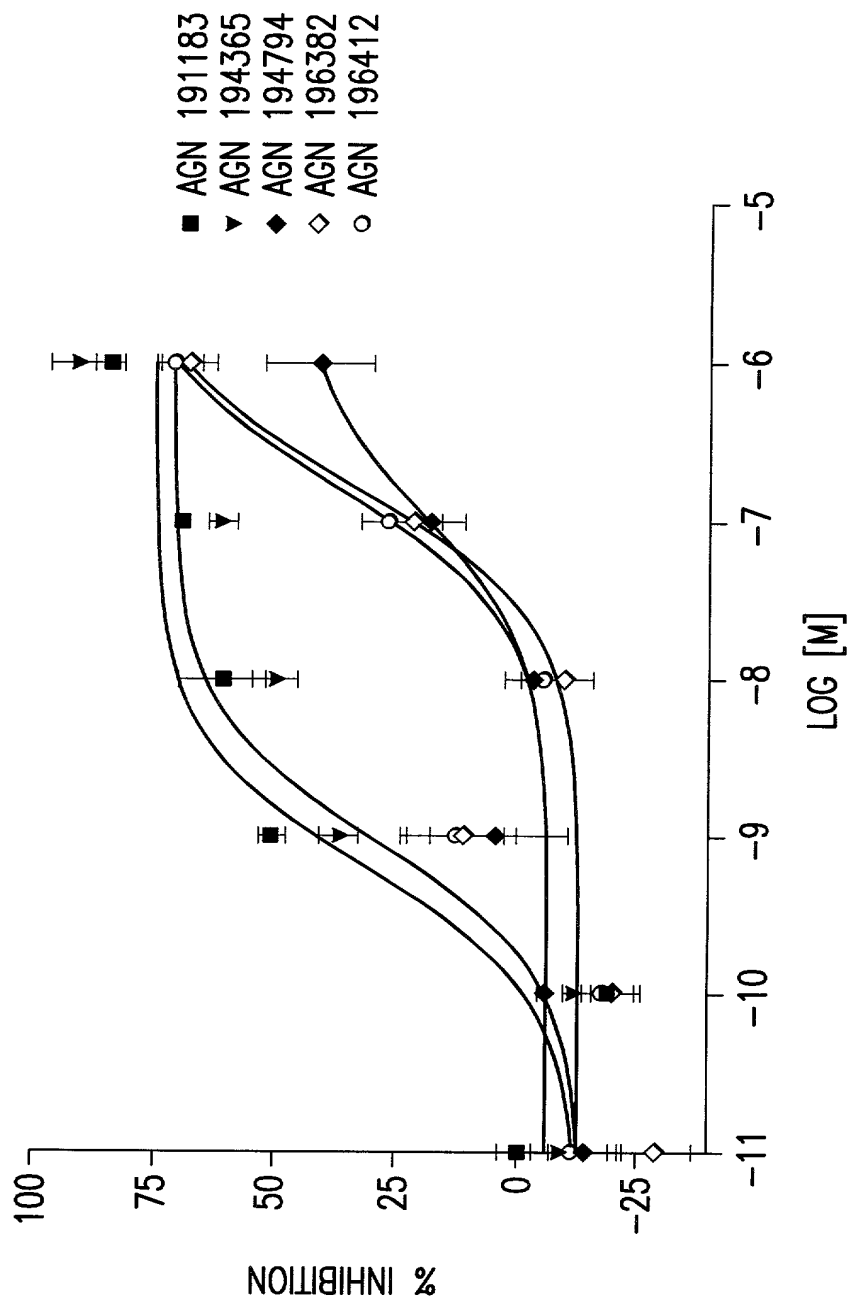
MASNSSSCPTPGGGHLNGYPVPPYAFFFPPMLGGLSPPGALTTLQHQLPVSGYSTPSPATIE
TQSSSSEEIVPSPPSPPPLPRIYKPCFVCQDKSSGYHYGVSACEGCKGFFRRSIQKNMVYTC
HRDKNCIINKVTRNRCQYCRLQKCFEVGMSKESVRNDRNKKKKEVPKPECSESYTLTPEVGE
LIEKVRKAHQETFPALCQLGKYTTNNSSEQRVSLDIDLWDKFSELSTKCIIKTVDFAKQLPG
FTTLTIADQITLLKAACLDILILRICTRYTPEQDTMTFSDGLTLNRTQMHNAGFGPLTDLVF
AFANQLLPLEMDDAETGLLSAICLICGDRQDLEQPDRVDMLQEPLLEALKVYVRKRRPSRPH
MFPKMLMKITDLRSISAKGAERVITLKMEIPGSMPPLIQEMLENSEGLDTLSGQPGGGGRDG
GGLAPPPGSCSPSLSPSSNRSSPATHSP

FIG.7A

MFDCMDVLSVSPGQILDFYTASPSSCMLQEKALKACFSGLTQTEWQHRHTAQSIETQSTSSE
ELVPSPPSPLPPPRVYKPCFVCQDKSSGYHYGVSACEGCKGFFRRSIQKNMIYTCHRDKNCV
INKVTRNRCQYCRLQKCFEVGMSKESVRNDRNKKKKETSKQECTESYEMTAELDDLTEKIRK
AHQETFPSLCQLAKYTTNSSADHRVRLDLGLWDKFSELATKCIIKIVEFAKRLPGFTGLTIA
DQITLLKAACLDILILRICTRYTPEQDTMTFSDGLTLNRTQMHNAGFGPLTDLVFTFANQLL
PLEMDDTETGLLSAICLICGDRQDLEEPTKVDKLQEPLLEALKIYIRKRRPSKPHMFPKILM
KITDLRSISAKGAERVITLKMEIPGSMPPLIQEMMENSEGHEPLTPSSSGNTAEHSPSISPS
SVENSGVSQSPLVQ

FIG.7B

MATNKERLFAAGALGPGSGYPGAGFPFAFPGALRGSPPFEMLSPSFRGLGQPDLPKEMASLS
VETQSTSSEEMVPSSPSPPPPPPRVYKPCFVCNDKSSGYHYGVSSCEGCKGFFRRSIQKNMVY
TCHRDKNCIINKVTRNRCQYCRLQKCFEVGMSKEAVRNDRNKKKKEVKEEGSPDSYELSPQL
EELITKVSKAHQETFPSLCQLGKYTTNSSADHRVQLDLGLWDKFSELATKCIIKIVEFAKRL
PGFTGLSIADQITLLKAACLDILMLRICTRYTPEQDTMTFSDGLTLNRTQMHNAGFGPLTDL
VFAFAGQLLPLEMDDTETGLLSAICLICGDRMDLEEPEKVDKLQEPLLEALRLYARRRRPSQ
PYMFPRMLMKITDLRGISTKGAERAITLKMEIPGPMPPLIREMLENPEMFEDDSSQPGPHPN
ASSEDEVPGGQGKGGLKSPA

FIG.7C

FIG. 8A

N-terminus   AF1   C4 Zn Fingers   CTE   E1   Dimer Contacts (hRXRα)   h9   AF2   C-terminus

hRXRα
hRARγ
rTRαl
hPPARγ
hERα
hPR

Ligand Binding Domain (|-Contact)

GM

DNA Binding Domain:

P-Box   CTE

(18) hRXRα   GKHYGVYSCEGCKGFFKRTVRKDL--TYTCRDNKDCLIDKRQRNRCQYCRYQKCLAMGM
(19) jfRXR   VKHYGVFACEGCKGFFKRSVRNNR--KYSCLGKRHCDTDKKSRNRCQYCRFQKCVQGM

(20) hTRβ   GYHYRCITCEGCKGFFRRTIQKNLHPSYSCKYEGKCVIDKVTRNQCQECRFKKCIYVGMATDLVLDDQSKRLAKRKLIEENREK

(21) hERα   GYHYGVWSCEGCKAFFKRSIQGH--NDYMCPATNQCTIDKNRRKSCQACRLRKCYEVGMMKGG

(22) rGR   GCHYGVLTCGSCKVFFKRAVEGQ--HNYLCAGRNDCIIDKIRRKNCPACRYRKCLQAGM

α-helices

E1 Region

(23)	Hrxrα	WAKRIPHFSELPLDDQVILL
(24)	jFRXR	WAKRLPHFRDLSIADQVLL
(25)	hTRα1	FAKKLPMFSELPCEDQIILL
(26)	hRARγ	FAKRLPGFTGLSIADQITLL
(27)	hPPARγ	YAKSIPGFVNLDLNDQVTLL
(28)	hLXR	FAKQLPGFLQLSREDQIALL
(29)	hVDR	FAKMIPGFRDLTSEDQIVLL
(30)	hER	WAKRVPGFVDLTLHDQVHLL
(31)	hGR	WAKAIPGFRNLHLDDQMTLL
(32)	hPR	WSKSLPGFRNLHIDDQITLI

[α-helix 3] [α-helix 4]

Heptad 9 (h9)

(33)	hRXRα	LLRLPALR
(34)	jFRXR	VILRIPALR
(35)	hTRα1	LLMKVTDLR
(36)	hRARγ	MLMKITDLR
(37)	hPPARγ	LLQKMTDLR
(38)	hLXR	MLMKLVSLR
(39)	hVDR	MIQKLADLR
(40)	hER	LLLILSHIR
(41)	hGR	LTKLLDSMH
(42)	hPR	LTKLLDNLH

[α-helix 10/11]

AF2 Domain

(43)	hRXRα	FLMEML
(44)	jFRXR	FLLDML
(45)	hTRα1	LFLEVF
(46)	hRARγ	LIREIL
(47)	hPPARγ	LLQEIW
(48)	hLXR	LLSEIW
(49)	hVDR	LVLEVF
(50)	hER	LLLEML
(51)	hGR	MLAEII
(52)	hPR	MISEVI

[α-helix 12]

FIG.8B